Phosphatidykinosital 3-Kinase and Mammalian Target of Rapamycin Pathway in Non–Small-Cell Lung Cancer

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The phosphatidykinosital 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin [mTOR] pathway is one of the most commonly deregulated pathways in cancer.[1–3] It is activated by the binding of extracellular growth factors to transmembrane receptor tyrosine kinases, including epidermal growth factor receptor (EGFR), HER2, insulin-like growth factor receptor, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor. Among the three known classes of phosphatidylinositaol-3-kinases (PI3Ks), the most frequently implicated in human cancer are class IA phosphatidylinositaol-3-kinases (PI3Ks), which are heterodimers of a p110 catalytic subunit and a p85 regulatory subunit, which inhibit p110 in the absence of receptor tyrosine kinase activation by ligand.[2,4,5]

PI3K/AKT/mTOR pathway targeting agents are currently being explored in lung cancer and advanced solid tumors. A good understanding of the safety profile of these agents is important in consideration of the fact that the PI3K/AKT/mTOR pathway plays a central role in the regulation of multiple cellular processes. To date, rash, hyperglycemia, and transaminase elevations seem to be class effects of PI3K/AKT/mTOR inhibition. Indeed, because PI3K/AKT/mTOR signaling plays a central role in insulin signaling, pathway inhibition can lead to insulin resistance.[6–8] The agents currently being investigated can be broken into multiple categories, depending on their target(s).

SUMMARY OF PRESENTATIONS

PI3K Inhibitors

BKM-120 (Novartis) is an oral highly specific inhibitor of class I PI3K. It has shown antiproliferative activity in tumoral cell lines and in xenografts bearing PI3K-mutated or PI3K wild-type tumors.[9] However, BKM-120 preferentially inhibits the proliferation of tumor cells with PIK3CA gene-bearing oncogenic mutations.[9] It has also shown proapoptotic effects in PI3K-mutated breast cancer cell lines.[10] In a phase I trial, BKM-120 was well tolerated and the most frequent grade 3–4 side effects, associated with doses of 80 mg or higher, were pruritus, mucositis, nausea, fatigue, anorexia, skin rash, hyperglycemia, altered mood, and diarrhea.[8] Increases in C-peptide were evident at all doses tested, whereas increases in glucose become more evident at doses of 80 mg or higher.[8] In the phase I trial, 16 of 20 patients treated at 80 to 150 mg showed 40% to 85% suppression of S6 phosphorylation in skin biopsies at the end of cycle 1.[8] Several phase I trials are ongoing, testing the association of BKM-120 with chemotherapy in solid tumors, including colorectal cancer, glioblastoma, and non–small-cell lung cancer (NSCLC). In particular, phase I trials in NSCLC are ongoing to test BKM-120 in combination with carboplatin and pemetrexed in advanced nonsquamous histology and in combination with erlotinib in *EGFR*-mutated lung adenocarcinoma patients previously sensitive to EGFR tyrosine kinase inhibitors.

The orally bioavailable PI3K inhibitor GDC-0941 (Genentech) selectively binds to PI3K isoforms p100alpha and p100delta (IC50 of 3 nM for both isoforms), and in an adenosine triphosphate (ATP)-competitive manner, inhibits the production of the secondary messenger phosphatidylinositol-3,4,5-trisphosphate and activation of the PI3K/protein kinase B (Akt) signaling pathway. Phase Ib clinical trials for metastatic NSCLC are ongoing, evaluating GDC-0941 in combination with bevacizumab. A phase II blinded, randomized trial is planned, which will test the association of GDC-0941 with chemotherapy with carboplatin and paclitaxel ± bevacizumab depending on histology (squamous or nonsquamous histology) in first-line metastatic NSCLC.

PX-866 is a potent orally available inhibitor of each of the four major forms of PI-3 kinase. In testing to date, it does not seem to have significant off-target effects. It is broadly active in preclinical tumor models, both as a single agent and in combinations with other targeted agents, chemotherapeutics and radiation.[11–14] The most important distinguishing characteristic of PX-866, however, is that it is the only irreversible inhibitor in development, which it achieves by covalently binding to the target. This property will facilitate sustained blockade of the PI-3 kinase signaling pathway, which may be important in achieving clinical benefit and in conferring dose and scheduling advantages, and may potentially result in few off-target effects. A phase I trial of single-agent PX-866 in solid tumors showed that a continuous schedule of administration had similar safety and better disease control than an intermittent schedule did. Most common side effects were diarrhea, nausea, vomiting, and reversible alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation.[14]

A phase I trial of PX-866 in combination with cetuximab in patients with metastatic colorectal and head and neck cancers showed 50% (4 of 9 patients) partial responses (PR), 38% (3 of 9 patients) stable disease (SD), and one disease progression.[15] A phase II trial of PX-866 in combination with docetaxel is planned in previously treated metastatic NSCLC and head and neck cancer.

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ON-01910 is a potent mitotic inhibitor that targets PI3K a and b isoforms. It affects translation of cap-dependent mRNAs and reduces level of Cyclin D, C-myc, and other regulatory proteins.[16] ON-01910 has shown to be well tolerated in the phase I trial in combination with gemcitabine in patients with advanced tumors with most frequent side effects of neutropenia, thrombocytopenia, and fatigue. It has shown good clinical activity in gemcitabine-pretreated pancreatic cancer patients and therefore it is currently in phase II trials in metastatic pancreatic cancer. One NSCLC patient was treated in the phase I trial with results of SD at 24 weeks.[17]

BAY 80–6946 is a potent and highly selective reversible pan-class I PI3K inhibitor with antitumor activity in a panel of preclinical models. A phase I dose-escalation multicenter study in patients with advanced solid tumors showed a maximum tolerated dose (MTD) of 0.8 mg/kg.[18] The most frequent adverse event was hyperglycemia with six of seven evaluable patients who received 200 mg/dL or more of insulin for glucose, but only within 24 hours of MTD. Other drug-related adverse events include grade 1/2 fatigue, nausea, vomiting, alopecia, diarrhea, mucositis and dysgeusia, and grade 2/3 anemia. Dose-limiting toxicity (DLT) was seen in one patient at 1.2 mg/kg consisting of grade 4 acute left ventricular dysfunction with lactic acidosis, liver dysfunction, and renal insufficiency, and grade 4 hyperglycemia, all recovering within several days. At MTD fluorodeoxyglucose (FDG) uptake was reduced by 23% in a liver lesion of a pancreatic patient and 40% in an NSCLC lesion.[18]

AKT Inhibitors

MK-2206 (Merck) is a first-in-class allosteric AKT1/2/3 inhibitor with evidence of preclinical activity and demonstrates synergistic activity in combination with cytotoxic agents (doxorubicin, gemcitabine, docetaxel, and carboplatin) in lung NCI-H460 cells. MK-2206 has also been shown to enhance erlotinib activity in erlotinib-sensitive and -resistant NSCLC cell lines and to resensitize cells rendered resistant through c-mesenchymal epithelial transition factor (MET) activation by hepatocyte growth factor (HGF).[19] In a phase I study, single-agent MK-2206 caused tumor regressions in a patient with pancreatic cancer with loss of phosphatase and tensin homolog (PTEN) expression and caused minor tumor regressions in one patient with melanoma and in one patient with a neuroendocrine tumor.[20] Common reversible drug-related toxicities included rash, nausea, fatigue, and hyperglycemia. MK-2206 is also undergoing evaluation in combination with chemotherapeutic agents and anti-HER2 therapy in breast cancer patients. In addition, on the basis of the preclinical rationale, the combination of MK-2206 and the MEK inhibitor AZD6244 (AstraZeneca) has been investigated and has shown encouraging activity, notably in NSCLC.[21]

MK-2206 in combination with MEK inhibition has shown more efficacy in a subset of lung cancer cell lines than single-agent therapy has.[22,23] Phase I combination therapy trial has been completed with side effects consisting mainly in skin toxicity,[20] and phase II trials are underway in metastatic NSCLC (the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination [BATTLE] 2 trial).

Other oral AKT inhibitors in phase I trials in cancer patients include GSK2141795, GSK2110183 (GlaxoSmithKline), GDC-0068 (Genentech), and LY2780301 (Eli Lilly), which also inhibits p70 S6 kinase. GSK2141795 was recently reported to demonstrate activity in anal, endometrial, and prostate cancers with reversible hyperglycemia, hypoglycemia, and stomatitis being the DLTs.[24]

mTOR Inhibitors

mTORC1 inhibitors are the most developed class of PI3K/AKT/mTOR pathway inhibitors and include everolimus, temsirolimus, and ridaforolimus. Everolimus and temsirolimus have been approved by the Food and Drug Administration for renal cell carcinoma, and everolimus has also been approved for subependymal giant cell astrocytoma associated with tuberous sclerosis and neuroendocrine tumors of pancreatic origin. Ridaforolimus is currently in a phase III study of sarcoma.

Everolimus has been studied in multiple clinical trials in patients with NSCLC, as single agent or in association with pemetrexed or erlotinib.[25,26] However, because of the relatively modest single-agent activity,[27] evidence does not support further testing in unselected patient populations. Results of phase II trials of everolimus in combination with chemotherapy or targeted agents have shown limited activity in NSCLC patients. In combination with erlotinib, everolimus has shown a progression-free survival of 2.9 months and 39% of disease control (complete response+ PR +SD).[25] The response rate for the combination of everolimus and gefitinib was 13% (all PR) in patients with advanced NSCLC who had either received no prior chemotherapy or had been previously treated with cisplatin or carboplatin and docetaxel or pemetrexed.[28] Similarly, only two patients (7%) achieved a PR when everolimus was given in combination with docetaxel as a second- or third-line treatment.[29] The combination of everolimus with pemetrexed has shown 12% of responses (PR +complete responses) in NSCLC patients who had disease progression after one previous treatment.[26]

A phase II trial of ridaforolimus in patients with *KRAS*-mutated NSCLC is currently ongoing showing promising results. In addition, clinical trials are underway for the combination of retaspimycin + everolimus in *KRAS*-mutant lung cancers and GDC0980 in malignant pleural mesotheliomas.

Limited data of temsirolimus as monotherapy in NSCLC have shown minimal efficacy. Selection of patients is essential for further clinical trials. A patient with NSCLC achieved a PR lasting for 12.7 months in a phase I study in patients with advanced solid tumors.[30] In a phase II study in patients with small-cell lung cancer, temsirolimus was administered as maintenance therapy after SD or in patients with disease that responded to induction therapy with cisplatin or carboplatin plus etoposide or irinotecan. In this study, temsirolimus did not seem to increase progression-free survival in these patients.[31] Clinical trials with other combination partners, such as neratinib and pemetrexed, are ongoing.

Published data from clinical studies with ridaforolimus in lung cancer are limited to a single patient achieving a PR in a phase I dose-escalation trial in patients with advanced

solid tumors.[32] Ongoing studies include a phase I combination trial with cetuximab in patients with head and neck cancer or NSCLC and a phase II trial in NSCLC patients with *KRAS* mutations.

BEZ235 is an orally available inhibitor with high selectivity for all three PI3K isoforms.[33] It also inhibits several other kinases including mTORC1 and mTORC2 kinase activity.[33] The first phase I clinical trial of BEZ235 in solid tumors showed two PRs: one in a patient with lung cancer and Cowden syndrome and the other in a heavily pretreated breast cancer patient.[34] Fourteen patients with different types of solid tumors achieved disease stabilization of 4 months or more.[34] Preclinical data on the combination of BEZ235 and RAD-001 has shown synergy with inhibition of tumor growth,[35] and a phase I trial testing this combination in solid tumors is currently in progress.

Development of mTOR kinase inhibitors targeting the function of mTORC1 and mTORC2 is ongoing.[36] On the basis of promising preclinical data, the mTORC1/2 inhibitors INK128 (Intellikine), AZD8055 (AstraZeneca), and OSI-027 (OSI Pharmaceuticals) are entering early clinical trials.[37,38] A phase I trial with OSI-027 reported disease stabilization in eight of 31 treated patients with DLTs of fatigue and decrease in left ventricular ejection fraction.[38]

FUTURE DIRECTIONS

The most recurrent issue in the development of PI3K/AKT/mTOR pathway inhibitors is the lack of clinical data in selected patient populations that carry mutations and/or other alterations of the pathway. Therefore, it is difficult to understand the role of these agents in a personalized therapy setting in these trials. Prospective screening modalities for pathway alterations are being incorporated in more recent trials of PI3K/AKT/mTOR pathway inhibitors. In fact, the inclusion criteria of the phase I study of BEZ235 (NCT01195376) require enrollment of patients with advanced solid tumors harboring *PIK3CA* mutation (or amplification) and/or a *PTEN* mutation and/or low or null PTEN expression. In studies of ridaforolimus (NCT00818675) and MK-2206 (NCT01021748), patients are required to have KRAS-driven NSCLC. In a study sponsored by the National Cancer Institute (NCT01306045), patients with lung cancer are prescreened and allocated into treatment groups based on the molecular profiles of their tumor biopsies. One of the arms of this study is investigating MK-2206, which will be used to treat patients with *PIK3CA*, *AKT*, or *PTEN* gene mutations. MK-2206 is also being studied in a similar study (BATTLE-2; NCT01248247). The results of these studies should help to better identify the patients who will be best suited for treatment with agents that target the PI3K/AKT/mTOR pathway.

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